CHOLBAM is a bile acid indicated for:

- Treatment of bile acid synthesis disorders due to single enzyme defects (SEDS). (1.1)
- Adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea or complications from decreased fat soluble vitamin absorption (1.2)

Limitation of use:
The safety and effectiveness of CHOLBAM on extracranial manifestations of bile acid synthesis disorders due to SEDs or PDs including Zellweger spectrum disorders have not been established. (1.3)

Dosage and Administration:
The recommended dosage is 10 to 15 mg/kg/day once daily or in two divided doses, in pediatric patients and adults. See prescribing information for weight-based dosing tables. (2.1)

- Discontinue CHOLBAM if liver function does not improve within 3 months of starting treatment, if complete biliary obstruction develops, or if there are persistent clinical or laboratory indicators of worsening liver function or cholestasis; continue to monitor liver function and consider restarting a lower dose when parameters return to baseline. (2.2, 5.1, 8.6)

Administration Instructions:
- Take with food. (2.3)
- Do not crush or chew the capsules. For patients unable to swallow the capsules, the capsules can be opened and the contents mixed with drink/food (2.3)

Dosage Forms and Strengths:
Capsules: 50 mg, 250 mg (3)

Contraindications:
None (4)

Warnings and Precautions:
Exacerbation of Liver Impairment: Monitor liver function and discontinue CHOLBAM if liver function worsens while on treatment. (5.1)

Adverse Reactions:
Most common adverse reactions (>1%) are diarrhea, reflux esophagitis, malaise, jaundice, skin lesion, nausea, abdominal pain, intestinal polyp, urinary tract infection, and peripheral neuropathy. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Manchester Pharmaceuticals, Inc. at 1-844-Cholbam or FDA at 1-800-FDA 1088 or www.fda.gov/medwatch.

Drug Interactions:
- Bile Salt Efflux Pump (BSEP) Inhibitors (e.g., cyclosporine): Avoid concomitant use; if concomitant use is necessary, monitor serum transaminases and bilirubin (7.1)
- Bile Acid Resins and Aluminum-Based Antacids: Take CHOLBAM at least 1 hour before or 4 to 8 hours (or at as great an interval as possible) after a bile acid binding resin or aluminum-based antacids. (2.3, 7.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: March 2015

Full Prescribing Information:

1 Indications and Usage
1.1 Bile Acid Synthesis Disorders due to Single Enzyme Defects
1.2 Peroxisomal Disorders including Zellweger Spectrum Disorders
1.3 Limitations of Use

2 Dosage and Administration
2.1 Dosage Regimen
2.2 Treatment Monitoring
2.3 Administration Instructions

3 Dosage Forms and Strengths
4 Contraindications

5 Warnings and Precautions
5.1 Exacerbation of Liver Impairment

6 Adverse Reactions
6.1 Clinical Trials Experience

7 Drug Interactions
7.1 Effects of Other Drugs on CHOLBAM

8 Use in Specific Populations
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment

*Sections or subsections omitted from the full prescribing information are not listed.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials may not necessarily reflect the rates observed with the drug in routine medical practice. Patients taking CHOLBAM should be monitored for worsening of liver function and concomitant deterioration of clinical condition. Such deterioration may require prompt reevaluation of the patient and possibly discontinuation of the drug. The following is a summary of adverse reactions that occurred in clinical trials for which CHOLBAM was administered as a single daily dose. Data are derived from 65 of 127 patients enrolled in trials of CHOLBAM, including 31 (21 SED and 10 PD) patients who rolled-over from Trial 1. Safety data are available for 3 years and 11 months of treatment. Adverse events were not collected systematically in either of these trials. Most patients received an oral dose of 10 to 15 mg/kg/d of CHOLBAM.

### Table 3: Most Common Adverse Reactions in Trials 1 and 2

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Overall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1</td>
<td>0</td>
<td>1%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>0</td>
<td>1*</td>
<td>1%</td>
</tr>
<tr>
<td>Intestinal Poly</td>
<td>0</td>
<td>1*</td>
<td>1%</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>0</td>
<td>1*</td>
<td>1%</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>0</td>
<td>1</td>
<td>1%</td>
</tr>
</tbody>
</table>

*Adverse reactions that occurred in new patients

### Drug Interactions

7.1. Effects of other drugs on CHOLBAM

Drug interactions with CHOLBAM mainly relate to agents capable of interrupting the enterohepatic circulation of bile acids.

Inhibitors of Bile Acids Transporters

Avoid concomitant use of inhibitors of the bile salt efflux pump (BSEP) such as cyclosporine. Concomitant medications that inhibit canalicular membrane bile acid transporters such as the BSEP may exacerbate accumulation of conjugated bile salts in the liver and result in clinical symptoms. If concomitant use is deemed necessary, monitoring of serum transaminases and bilirubin is recommended.

Bile Acid Binding Resins

Bile acid binding resins such as cholestyramine, colestipol, or colesvelam adsorb and reduce bile acid absorption and may reduce the efficacy of CHOLBAM. Take CHOLBAM at least 1 hour before or 4 to 6 hours (or at as great an interval as possible) after a bile acid binding resin [see Dosage and Administration (2.4)].

Aluminum-Based Antacids

Aluminum-based antacids have been shown to adsorb bile acids in vitro and can reduce the bioavailability of CHOLBAM. Take CHOLBAM at least 1 hour before or 4 to 6 hours (or at as great an interval as possible) after an aluminum-based antacid [see Dosage and Administration (2.4)].

### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy surveillance program that monitors pregnancy outcomes in women exposed to CHOLBAM during pregnancy. Women who become pregnant during CHOLBAM treatment are encouraged to enroll. Patients or their healthcare provider should call 1-844-202-0000 or 1-844-202-6262 to enroll.

### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Clinical safety experience with CHOLBAM consists of:

- Trial 1: a non-randomized, open-label, single-arm trial of 50 patients with bile acid synthesis disorders due to SEDs and 29 patients with PDs including Zellweger spectrum disorders. Safety data are available over the 18 years of the trial.
of bile.

Bile Salt Efflux Pump (BSEP), and then released into the small intestine, along with other components

CoA: amino acid N-acetyltransferase. Conjugated cholic acid is actively secreted into bile mainly by the

In the liver, cholic acid is conjugated with glycine or taurine by bile acid-CoA synthetase and bile acid-

mainly in conjugated forms.

Cholic acid is absorbed by passive diffusion along the length of the gastrointestinal tract. Once

Orally administered cholic acid is subject to the same metabolic pathway as endogenous cholic acid.

Endogenous bile acids including cholic acid enhance bile flow and provide the physiologic feedback

cholestasis. Bile acids facilitate fat digestion and absorption by forming mixed micelles, and facilitate

Cholic acid is a primary bile acid synthesized from cholesterol in the liver. In bile acid synthesis

contains gelatin, red iron oxide and titanium dioxide and the size 0 shells contain gelatin and titanium

orange or size 0 white opaque gelatin capsules, respectively. Inactive ingredients in CHOLBAM include

and is sparingly soluble in 0.1 M NaOH at 20°C. It is soluble in glacial acetic acid, alcohols and acetone.

Cholic acid is a white to off-white powder. It is practically insoluble in water and in 0.1 M HCl at 20°C

ChOLBAM overdose. Continue to monitor laboratory parameters of liver function and consider

In the event of overdose the patient should be monitored and treated symptomatically.

11 DESCRIPTION

Cholic acid is a bile acid produced by the liver where it is synthesized from cholesterol. The chemical formula is C\textsubscript{24}H\textsubscript{40}O\textsubscript{6}, the molecular weight is 408.57 and the chemical structure is:

\[
\text{CH}_3
\begin{array}{c}
\text{OH} \\
\text{O} \\
\text{OH} \\
\text{CH}_2
\end{array}
\begin{array}{c}
\text{OH} \\
\text{OH} \\
\text{O} \\
\text{CH}_3
\end{array}
\begin{array}{c}
\text{O} \\
\text{CH}_2
\end{array}
\begin{array}{c}
\text{O} \\
\text{CH}_2
\end{array}
\begin{array}{c}
\text{OH} \\
\text{OCOCH}_3
\end{array}
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{OH}
\end{array}
\begin{array}{c}
\text{OH} \\
\text{OH}
\end{array}

Cholic acid is a white to off-white powder. It is practically insoluble in water and in 0.1 M HCl at 20°C

and is sparingly soluble in 0.1 M NaOH at 20°C. It is soluble in glacial acetic acid, alcohols and acetone.

A saturated solution in water at 20°C has a pH of 4.4. CHOLBAM capsules contain 50 mg or 250 mg of cholic acid as the active ingredient in size 2 Swedish orange or size 0 white opaque gelatin capsules, respectively. Inactive ingredients in CHOLBAM include

silkicized microcrystalline cellulose, magnesium stearate and hard gelatin capsules. The size 2 shells

contain gelatin, red iron oxide and titanium dioxide and the size 0 shells contain gelatin and titanium
dioxide. CHOLBAM is administered orally.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cholic acid is a primary bile acid synthesized from cholesterol in the liver. In bile acid synthesis

disorders due to SEEDs in the biosynthetic pathway, and in PDs including Zellweger spectrum disorders, deficiency of primary bile acids leads to unregulated accumulation of intermediate bile acids and

cholestasis. Bile acids facilitate fat digestion and absorption by forming mixed micelles, and facilitate absorption of fat-soluble vitamins in the intestine.

Endogenous bile acids including cholic acid enhance bile flow and provide the physiologic feedback

inhibition of bile acid synthesis. The mechanism of action of cholic acid has not been fully established;

however, it is known that cholic acid and its conjugates are endogenous ligands of the nuclear

receptor, farnesoid X receptor (FXR). FXR regulates enzymes and transporters that are involved in bile

acid synthesis and in the enterohepatic circulation to maintain bile acid homeostasis under normal

physiologic conditions.

12.3 Pharmacokinetics

Orally administered cholic acid is subject to the same metabolic pathway as endogenous cholic acid.

Cholic acid is absorbed by passive diffusion along the length of the gastrointestinal tract. Once

absorbed, cholic acid enters into the body's bile acid pool and undergoes enterohepatic circulation

mainly in conjugated forms.

In the liver, cholic acid is conjugated with glycine or taurine by bile acid-CoA synthetase and bile acid-

CoA: amino acid N-acetyltransferase. Conjugated cholic acid is actively secreted into bile mainly by the

Bile Salt Efflux Pump (BSEP), and then released into the small intestine, along with other components of bile.

Conjugated cholic acid is mostly re-absorbed in the ileum mainly by the apical-sodium-dependent-bile

acid transporter, passed back to the liver by transporters including sodium-taurocholate cotransporting

polypeptide and organic anion transport protein and enters another cycle of enterohepatic circulation.

Any conjugated cholic acid not absorbed in the ileum passes into the colon where deconjugation and 7-dehydroxylase are mediated by bacteria to form cholic acid and deoxycholic acid which may be

re-absorbed in the colon or excreted in the feces. The loss of cholic acid is compensated by de-novo

synthesis of cholic acids from cholesterol to maintain the bile acid pool in healthy subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genetic toxicology, and nonclinical fertility studies have not been performed with cholic acid.

13.2 Animal Toxicology and/or Pharmacology

In the PEX2\textsuperscript{2} mouse model of peroxisomal disorders, feeding with a combination of cholic acid and

ursodeoxycholic acid normalized C\textsubscript{3} bile acid concentrations in bile to that of untreated control animals.

Although growth was only mildly improved, there was near complete normalization of stool fat content,

resolution of steatorrhea, and improved survival. Bile acid feeding reduced the number of cholestatic

deposits in bile ducts and alleviated cholangitis, but exacerbated the degree of hepatic steatosis and

mitochondrial and cellular damage in the peroxisome-deficient livers of these animals.

14 CLINICAL STUDIES

14.1 Bile Acid Synthesis Disorders due to Single Enzyme Defects

The effectiveness of CHOLBAM at dosages of 10 to 15 mg/kg per day in patients with SEEDs

was assessed in:

• Trial 1: a non-randomized, open-label, single-arm trial in 50 patients over an 18 year period.

• Trial 2: an extension trial of 12 new patients along with 21 patients who rolled-over from Trial 1

(n=33 total). Efficacy data are available for 21 months of treatment.

• A published case series of 15 patients.

Enrollment criteria in Trials 1 and 2 were based on abnormal urinary bile acid by Fast Atom

Bomardionization - Mass Spectrometry (FAB-MS) analysis. Pre- and post-treatment liver biopsies were performed in a limited number of patients. Documentation of adherence to treatment, concomitant medications and response to treatment were incomplete during Trial 1. Additional interventions in some patients included supplementation with fat-soluble vitamins, as dictated by the patient's clinical signs and symptoms.

Trials 1 and 2

On average, patients were 4 years of age at the start of cholic acid treatment (range three weeks to 36

years). The majority of patients were treated for an average of 310 weeks (6 years). Patient ages at the end of treatment ranged from 19 to 36 years.

These trials were carried out over many years and data are not available on all patients. Thirty-

nine patients in Trial 1 and 5 new patients in Trial 2 received at least one dose of CHOLBAM and

had sufficient data available to assess baseline liver function and effects of CHOLBAM treatment. A

responder analysis was performed to determine the response to treatment with CHOLBAM.

Response to CHOLBAM treatment was assessed by the following laboratory criteria:

(1) ALT or AST values reduced to less than 50 U/L, or baseline levels reduced by 80%;

(2) total bilirubin values reduced to less than or equal to 1 mg/dL; and

(3) no evidence of cholestasis on liver biopsy;

and the following clinical criteria:

(1) body weight increased by 10% or stable at greater than the 50th percentile; and

(2) survival for greater than 3 years on treatment or alive at the end of Trial 2

CHOLBAM responders were defined as patients who either:

(1) met at least two laboratory criteria and were alive at the last follow-up;

(2) met at least one laboratory criterion, had increased body weight and were alive at the last follow-up.

Overall, 28 of 44 patients (64%) were responders. The breakdown by defect type is as follows:

| Table 4: Response to CHOLBAM Treatment by Type of Single Enzyme Defect |
|-----------------------------|-----------------------------|
| Single Enzyme Defect | Responders/Number Treated (%) |
| 3\textsubscript{3}-HSD | 22/37 (69%) |
| AKR1D1 | 3/4 (75%) |
| CTX | 2/2 (100%) |
| AMACR | 1/1 (100%) |
| CYP7A1 | N/A* |
| Smith-Lemli-Opitz | N/A* |

*N/A indicates no evaluable patients in the defect subgroup represented.

Among SEED responsive patients, 45% of the responders met the two clinical criteria plus 1 to 3

laboratory criteria and 55% met the weight criteria.

Only six patients had pre- and post-treatment liver biopsies in Trial 1. Where biopsies were available,

pre-treatment biopsies showed varying degrees of inflammation, bridging fibrosis, and giant cell

formation. Post-treatment biopsies generally showed reduced or absent inflammation and reduced or

absent giant cell formation, Fibrosis remained but did not progress. It is difficult to evaluate long term survival in patients with SEEDs since there is little natural history survival data for comparison. Overall, 41 of 62, or 67%, of patients with SEEDs survived greater than 3

years from trial entry. Thirteen of these 41 patients, or 32%, were “long-term” survivors (range of 10 to 24 years on treatment).

Four patients in Trial 1 underwent liver transplant, including two patients diagnosed with AKR1D1

deficiency, one with 3\textsubscript{3}-HSD deficiency, and one with CYP7A1 deficiency and two patients in Trial 2, both with AKR1D1.

CHOLBAM’s effects on enterohepatic manifestations of SEEDs, such as neurologic symptoms are not

established.

Case Series

A published report of a case series described 15 patients with SEEDs; thirteen were diagnosed with

3\textsubscript{3}-HSD deficiency and two with AKR1D1 deficiency by mass spectrometry and gene sequencing. All
patients were treated with cholic acid with a median duration of treatment of 12.4 years (range 5.6 to 15 years). Therapy started at a median age of 3.9 years (range 0.3 to 13.1 years). The mean dose at the start of cholic acid treatment was 13 mg/kg and the mean dose at last follow up was 6 mg/kg. Eight patients were initially treated with oral ursodeoxycholic acid prior to receiving a diagnosis of bile acid synthesis defect, after which they were switched to cholic acid. Initial signs and symptoms included jaundice, hepatosplenomegaly, steatorrhea, or symptoms related to deficiency of a fat soluble vitamin (K, D or E).

Of the 8 patients who received ursodeoxycholic acid initially, the six with 3β-HSD deficiency demonstrated marked clinical improvement. Following treatment with cholic acid, all patients experienced resolution of their pre-existing jaundice and steatorrhea, and all but one experienced resolution of hepatosplenomegaly. Weight and height improved and sexual maturation progressed normally in all patients. Liver biopsies were performed in 14 patients after at least 5 years of cholic acid treatment and all showed resolution of cholestasis. In one patient with 3β-HSD deficiency, biliary bile acid analysis while on cholic acid therapy showed enrichment of the bile with cholic acid.

14.2 Peroxisomal Disorders including Zellweger Spectrum Disorders

The effectiveness of CHOLBAM at a dosage of 10 to 15 mg/kg per day in patients with PDs including Zellweger spectrum disorders was assessed in patients in the same trials described in section 14.1.

- Trial 1 treated 29 patients with PDs over an 18 year period.
- Trial 2 treated 2 new patients along with 10 patients who rolled-over from Trial 1 (n=12 total).

Efficacy data are available from Trial 2 for 21 months of treatment.

Additional efficacy data were obtained from published case reports of 3 patients.

 Enrollment criteria in Trials 1 and 2 were based on abnormal urinary bile acids analysis by Fast Atom Bombardment ionization - Mass Spectrometry (FAB-MS) and a neurologic exam. Most patients received concomitant DHC (dihydroxy-chenodeoxy) and Vitamins A, D, E and K. Documentation of adherence to treatment, concomitant medications and response to treatment were incomplete during Trial 1.

Trials 1 and 2

The majority of patients (80%, 25/31) were less than 2 years of age at the start of CHOLBAM treatment (range 3 weeks to 10 years). The majority of patients were treated for an average of 254 weeks (4.8 years).

Sufficient data were available to assess baseline liver function and effects of CHOLBAM treatment in 23 patients in Trial 1 and in one new patient in Trial 2. A responder analysis was performed in the patients who had received at least one dose of CHOLBAM and had sufficient data available to assess baseline liver impairment.

Response to CHOLBAM treatment was assessed by the following laboratory criteria:

1. ALT or AST values reduced to less than 50 U/L, or baseline levels reduced by 80%;
2. total bilirubin values reduced to less than or equal to 1 mg/dL; and
3. no evidence of cholestasis on liver biopsy;

and the following clinical criteria:

1. body weight increased by 10% or stable at greater than the 50th percentile; and
2. survival for greater than 3 years on treatment or alive at the end of Trial 2

CHOLBAM responders were defined as patients who either:

1. met at least two laboratory criteria and were alive at the last follow-up; or
2. met at least one laboratory criterion, had increased body weight and were alive at the last follow-up.

Overall, 11 of 24 patients (46%) were responders. The breakdown by disorder is as follows:

Table 5: Response to CHOLBAM Treatment by Type of Peroxisomal Disorders including Zellweger Spectrum Disorders

<table>
<thead>
<tr>
<th>Peroxisomal Disorder</th>
<th>Responders/Number Treated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Adrenoleukodystrophy</td>
<td>3/6 (50%)</td>
</tr>
<tr>
<td>Generalized Peroxisomal Disorder</td>
<td>1/7 (100%)</td>
</tr>
<tr>
<td>Refsum Disease</td>
<td>3/4 (75%)</td>
</tr>
<tr>
<td>Zellweger Syndrome</td>
<td>3/8 (38%)</td>
</tr>
<tr>
<td>Peroxisomal Disorder, Type Unknown</td>
<td>1/5 (20%)</td>
</tr>
</tbody>
</table>

Among responsive patients with PDs, 38% of the responders met the two clinical criteria plus 1 to 3 laboratory criteria and 63% met the weight criteria. There were no PD patients that underwent liver transplant.

No evidence of improvement in survival over that seen in historical controls could be demonstrated from the data presented. Overall, 13 of 31, or 42%, of patients survived greater than 3 years from the time of trial entry. Eight of these 13 patients, or 62% were “long-term” survivors (range of 10 to 17 years on treatment).

Nine patients had both pre- and post-treatment liver biopsies. One patient showed improvement in histology, while the majority of patients remained unchanged. Two patients demonstrated worsening histology, which was consistent with a worsening of other liver laboratory parameters (bilirubin, serum transaminase values).

CHOLBAM’s effects on extrahepatic manifestations of PDs including Zellweger spectrum disorders, such as neurologic symptoms are not established. One patient, who did not have cholestasis on pre-treatment liver biopsy, developed cholestasis on treatment with CHOLBAM and subsequently died.

16 HOW SUPPLIED/STORAGE AND HANDLING

50 mg Capsules

CHOLBAM capsules are available as two-piece gelatin capsules with a Swedish orange cap imprinted with “250mg” and Swedish orange body imprinted with “ASK001”. The capsules contain a white or off-white powder and are supplied in bottles of:

- 90 capsules (NDC 46043-002-02)

Storage and Handling

Store at 20–25°C (69-77°F), excursions permitted between 15–30°C (59-86°F). [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Exacerbation of Liver Impairment

- Advise patients that they will need to undergo laboratory testing periodically while on treatment to assess liver function.
- Advise patients that CHOLBAM may worsen liver impairment and that they should immediately report to their health care provider any symptoms associated with liver impairment (e.g., skin or the whites of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleeding or bruising occurs more easily than normal, or increased lethargy).

Administration

Advise patients:

- to take CHOLBAM with food.
- to take CHOLBAM at least one hour before or 4 to 6 hours after taking a bile acid binding resin or an aluminum-based antacid.
- not to crush or chew the capsules.

For infants and children who cannot swallow capsules, the capsules can be opened and the contents mixed with either infant formula or expressed breast milk (for younger children), or soft food such as mashed potatoes or apple puree (for older children and adults) in order to mask any unpleasant taste.

1. Hold the capsule over the prepared liquid/food, gently twist open, and allow the contents to fall into the liquid/food.
2. Mix the entire capsule contents with one or two tablespoonsfuls (15 mL to 30 mL) of infant formula, expressed breast milk, or soft food such as mashed potatoes or apple puree.
3. Stir for 30 seconds.
4. The capsule contents will remain as fine granules in the milk or food, and will not dissolve.
5. Administer the mixture immediately.

Pregnancy Registry

Advise patients there is a pregnancy surveillance program that monitors pregnancy outcomes in women exposed to CHOLBAM during pregnancy [see Use in Specific Populations (8.1)].

CHOLBAM™ is a trademark of Retrophin, Inc.

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Manufactured by:

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38300 Bourgoin-Jallieu, France

Manufactured for:

Manchester Pharmaceuticals, Inc. a wholly owned subsidiary of Retrophin, Inc. San Diego, CA 92130

For further information, please call 844-246-5226